Methotrexate therapy in polymyositis

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Polymyositis, an inflammatory disorder of skeletal and occasionally cardiac muscle, may present as a myopathy alone, as one manifestation of a multi-system disorder, especially systemic sclerosis (Medsker, Rodnan, Moossy, and Vester, 1968; Thompson, Bluestone, Bywaters, Dorling, and Johnson, 1969; Brock, 1934), systemic lupus erythematosus (White, 1959; Dubois, 1966), and Sjögren's syndrome (Bunim, 1961), or in association with neoplastic lesions (Williams, 1959; Pearson, 1969). Weakness, particularly of the limb girdle musculature, is the dominant clinical manifestation, pain and tenderness being far less common (Pearson, 1962, 1966; Shulman, 1969).

Irrespective of the clinical setting, histologically one finds infiltration of the affected muscle bundles with inflammatory cells, oedema separating myofibrils, and varying degrees of fibrillar fragmentation, degeneration, and regeneration. Loss of muscle mass is the eventual outcome unless effective suppression of the inflammatory process is achieved.

Except for the response to surgery in those with resectable malignant lesions, corticosteroids are the drugs of choice (Pearson, 1966, 1969; Vignos, Bowling, and Watkins, 1964; Winkelman, Mulder, Lambert, Howard, and Diessner, 1968). A significant number of patients, however, resist adequate control with these agents or are unable to tolerate the required dosage level. Improvement in steroid-refractory polymyositis has been reported after addition of the folic acid antagonist, Methotrexate (Malaviya, Many, and Schwartz, 1968; Sokoloff, Goldberg, and Pearson, 1971). It is our purpose to report five additional patients with steroid-refractory polymyositis treated with Methotrexate, emphasizing the drug toxicity as well as therapeutic response which characterized the majority.

Diagnostic criteria

From July, 1970, to December, 1971, sixteen patients with polymyositis were admitted to the Connective Tissue Unit of the Good Samaritan Hospital. The diagnosis of polymyositis was established if, in the absence of a family history of muscle disease, two of the following three criteria were met:

- (1) A history of proximal muscle weakness, confirmed by physical examination;
- (2) Elevation of one or more muscle enzymes;
- (3) Muscle biopsy with characteristic histology.

In all sixteen patients proximal muscle weakness and elevated muscle enzymes were present. Twelve patients satisfied all three criteria. In three patients (10, 15, and 11) a muscle biopsy was normal despite clinical and chemical evidence of myositis. In one (16) no biopsy was obtained.

Patient classification

GROUP I

Six patients (1-6) had polymyositis alone, without skin changes of dermatomyositis, features of other connective tissue diseases, or evidence of malignancy.

GROUP II

In eight patients (7-14), polymyositis was a dominant manifestation of a multisystem connective tissue disorder, most commonly systemic sclerosis (7-12). One patient (13) had systemic lupus erythematosus with myositis confined to the pelvic girdle and lower extremities. One (14) had an 'overlap' syndrome with, in addition to myositis, Raynaud's phenomenon, sclerodactyly, polyarthritis, pulmonary fibrosis, keratoconjunctivitis sicca, and antinuclear factors.

GROUP III

Two patients (15, 16) had polymyositis in association with malignancy; one had carcinoma of the oesophagus, and the other an adenocarcinoma of the carcinoid type

(bronchial adenoma) in the lung. The latter (16) was of unusual interest in that she evidenced sclerodermatous skin changes over the upper extremities and face, without Raynaud's phenomenon or features other than the myopathy to support a diagnosis of systemic sclerosis.

Selection of patients for Methotrexate

The inflammatory myopathy was managed successfully with corticosteroids in ten (63 per cent.) of the sixteen patients, including the two with neoplasm which was respectable in one (16). One patient (13) with steroid-refractory myositis refused Methotrexate. The five remaining patients received Methotrexate in addition to steroids, four in Group I and one with systemic sclerosis in Group II. The clinical details of these Methotrexate-treated patients are here reported.

Case reports

Case 3, a 69-year-old retired brewery worker, was admitted to hospital in March, 1970, with muscle weakness of 4 months' duration. After the gradual onset of weakness in the lower extremities, he developed weakness in the upper extremities and difficulty swallowing associated with a 50 lb weight loss.

Physical examination

The patient was a well-developed white male who appeared chronically ill. There was marked wasting and weakness in the proximal muscles of the upper and lower extremities without muscle tenderness or pain on stretch. The remainder of the examination was normal except for the stigmata of chronic obstructive pulmonary disease and mild congestive heart failure.

Laboratory investigations

Haematocrit 44 per cent.; white blood cell count (WBC) 12,000/mm.³ with a normal differential; platelet count, 250,000/mm.³; erythrocyte sedimentation rate 33 mm./hr.

T4 by column, 4.3 mcg per cent. was normal. Latex fixation, Waaler-Rose, L.E. cell, and immunofluorescent antinuclear antibody tests negative. Muscle enzymes: SGOT 58, SGPT 75, LDH 104, CPK 168, and aldolase 10. Electromyogram demonstrated low amplitude and short duration polyphasic potentials in proximal muscles.

A search for occult malignancy was negative.

Course

Muscle biopsy confirmed the compression of active polymyositis, and the patient was treated with prednisone 100 mg./day. The course was complicated by a left lower lobe pneumonia due to *Strongyloides stercoralis* which responded to thiabendazole therapy; however, larvae persisted in the stool despite several courses of this drug.

After 2 weeks prednisone was tapered to 60 mg./day and at one month the enzymes began to improve, with SGOT 39, SGPT 39, LDH 198, CPK 104, aldolase 1.7. The patient's muscle strength slowly improved during his 3 months in hospital and all muscle enzymes returned to normal. He was discharged in June, 1970, on 30 mg. prednisone daily.

Profound muscle weakness and fatigability returned 2 months later, and he was re-admitted in August, 1970. The muscle enzymes were markedly elevated, with SGOT 86, SGPT 41, LDH 740, CPK 1110, aldolase 34. A repeat search for tumour was unrevealing. Prednisone was increased to 60 mg./day, but in the ensuing month muscle strength further deteriorated and muscle enzymes remained elevated, with SGOT 53, SGPT 48, LDH 600, CPK 520, aldolase 18. On September 9, 1970, Methotrexate therapy was begun with an initial intravenous dose of 25 mg. followed by weekly 50 mg. intravenous injections. Prednisone was continued at 60 mg./day. After 1 month of Methotrexate, muscle enzyme levels had decreased to SGOT 44, SGPT 45, LDH 490, CPK 161, aldolase 4.9. Buccal ulcers appeared but cleared rapidly when one weekly dose was withheld. Prednisone was tapered to 50 mg./day. After 2 months, muscle strength began to improve, SGOT 16, SGPT 30, LDH 440, CPK 59, aldolase 1.5. Over the next 2 months muscle enzymes remained normal and prednisone was tapered to 15 mg./day. Muscle strength improved so that he could climb two flights of stairs. He was discharged in late December on 50 mg. Methotrexate intravenously at 2-week intervals and prednisone 15 mg./day. With a rise in enzymes in February, 1971, to SGOT 39, CPK 355, aldolase 22.3, Methotrexate was increased to 50 mg. weekly; the enzymes remained elevated but without deterioration in muscle strength.

The patient was again admitted to hospital in April, 1971, with renal colic and *Proteus* sepsis which responded well to antibiotic therapy. Re-evaluation of the liver function revealed an increase in alkaline phosphatase and 5' nucleotidase. A liver scan revealed diffuse hepatomegaly without focal defects. The patient refused a liver biopsy. Because of possible Methotrexate hepatotoxicity, this drug was discontinued. Prednisone was increased from 15 to 30 mg./day, which proved to be the required maintenance level. Since discontinuing Methotrexate and increasing steroids, however, his muscle strength has progressively deteriorated.

Case 4, a 47-year-old hospital housekeeper, was entirely well until September, 1969, when she noted weakness of the upper extremities and, one week later, difficulty in rising from chairs and climbing stairs. One month later nasal speech developed, and she began to regurgitate liquids through the nose. Muscle and joint pain on exercise, and a 24-lb weight loss occurred during the 2 months before admission to hospital in November, 1969.

Physical examination

The patient was a chronically ill black female. There was patchy frontal alopecia and hyperpigmentation over the metacarpophalangeal and proximal interphalangeal joints. There was no sclerodermatous thickening. Musculoskeletal evaluation revealed nasal speech with poor palatal and pharyngeal contractions, marked proximal weakness in the muscles of the neck, shoulder, and pelvic girdles, and tenderness in the deltoids, biceps, and quadriceps muscles. There was tenderness of the first three proximal interphalangeal joints bilaterally and both wrists. Small effusions were present in both knees. The remainder of the examination, including that of the nervous system, gave normal results.

Laboratory investigations

Haematocrit 36 per cent., WBC 7200/mm.³ with a normal differential count; platelet count 255,000/mm.³; erythrocyte sedimentation rate 46 mm./hr. T4 by column was normal, 3.1 mcg per cent. Latex-fixation positive 1/160. Waaler-Rose negative. Tests for L.E. cells and antinuclear antibody were negative. Muscle enzymes revealed SGOT 575, SGPT 125, LDH 1260, and CPK 2624. A left deltoid muscle biopsy showed an intense inflammatory infiltrate consisting of plasma cells, lymphocytes, and macrophages surrounding the blood vessels without vascular wall necrosis. A barium swallow demonstrated markedly diminished peristalsis in the upper oesophagus, and a ciné oesophagogram confirmed weakness in the pharyngeal constrictors. A search for occult malignancy was negative.

Course

Corticosteroid therapy was begun with 80 mg./day prednisone. After 1 month voice and swallowing abnormalities were gone and proximal extremity weakness had improved. SGOT 180, LDH 790, and CPK 1770. Prednisone was reduced to 60 mg./day. After 3 months muscle strength approached normal although enzymes remained elevated, SGOT 40, LDH 197, CPK 585. Prednisone had been tapered to 30 mg./day.

In November, 1970, after 11 months of therapy, prednisone was reduced to 25 mg./day, and enzymes began to increase. In February, 1971, the patient again developed aching in the thighs and difficulty in rising from a chair. She was re-admitted to hospital, and on examination, there was marked weakness in the strap muscles of the neck, shoulder abductors, triceps, quadriceps, and psoas without muscle tenderness. The remainder of the physical examination was normal. Muscle enzymes: SGOT 19, SGPT 27, LDH 650, CPK 420, aldolase 8.7.

Methotrexate therapy was initiated with weekly 25 mg. intravenous injections. Prednisone was continued at 25 mg./day. After 3 weeks of Methotrexate therapy, the weakness was minimal, and enzymes SGOT 12, SGPT 11, CPK 243, LDH 312, aldolase 6.1. After 5 weeks there was no demonstrable muscle weakness, but the CPK remained elevated at 177 and the LDH at 311. At 11 weeks all muscle enzymes were normal.

The patient was maintained on weekly Methotrexate for 5 months, and then on bi-weekly injections over the next 5 months. At the present time, a maintenance schedule of 25 mg. at 3-week intervals is continued, in conjunction with prednisone, 25 mg./day. Muscle strength has remained normal, and muscle enzymes have also been normal except for the CPK which varies from 60 to 80 units. There has been no clinical or laboratory evidence of drug toxicity.

Case 7, a 19-year-old black college student, began to develop progressive weakness in both arms in March, 1969. In July, her private physician recorded proximal muscle weakness in both the upper and the lower extremities, muscle enzyme elevation, and a muscle biopsy consistent with active polymyositis. Prednisone 40 mg./day was begun and tapered to 20 mg./day over 5 months. Muscle weakness continued, and she was hospitalized in November, 1969. In addition to moderate proximal weakness, sclerodactyly was present. SGOT 154, CPK

4471, aldolase 22.7. Prednisone 80 mg./day was instituted, and in 5 months all muscle enzymes and muscle strength returned to normal.

In June, 1970, Raynaud's phenomenon and significant hypertension with diastolic pressures of 130-160 mm. Hg developed. In addition to sclerodactyly, the skin over the hands, arms, face and anterior chest was sclerodermatous. Fine crepitant rales were present in both lower lung fields. Muscle strength and other investigations, including muscle enzymes, were normal. A repeat muscle biopsy demonstrated fibrosis between muscle bundles and a few regenerating myofibrils. Pulmonary function studies revealed a reduced vital capacity, Fev¹, and CO diffusing capacity. Motility studies demonstrated aperistalsis of the distal two-thirds of the oesophagus and reduced amplitudes of contractions in the upper oesophagus and pharynx. Prednisone was tapered to 45 mg./day, and hypertension was controlled with guanethidine.

By December, 1970, prednisone had been tapered to 20 mg./day. Proximal limb-girdle muscle weakness recurred, and muscle enzymes increased, and the patient was re-admitted in February, 1971, for immunosuppressive therapy.

Physical examination

The patient was markedly Cushingoid. Vital signs including blood pressure were normal. The sclerodermatous skin changes were unchanged. End-inspiratory dry rales were present at both lung bases. The heart was enlarged, with S2P louder than S2A. There was marked proximal muscle weakness in the upper and lower extremities, and bilateral thigh tenderness. The remainder of the examination was normal.

Laboratory investigations

Haematocrit 37 per cent., WBC 16,500/mm.³ with 7 per cent. juveniles, 87 per cent. neutrophils, 5 per cent. lymphocytes, and 1 per cent. monocytes. Platelets 360,000/mm.³. Erythrocyte sedimentation rate 36 mm./hr. Latex, Waaler-Rose, L.E. cell, and immunofluorescent antinuclear antibody tests were negative. All muscle enzymes were elevated: SGOT 125, SGPT 52, LDH 1310, CPK 2610, aldolase 30.7.

Course

Oral Methotrexate was begun, since the thickened skin precluded chronic intravenous therapy. A daily dose of 5 mg. for 4 days (20 mg.) was initiated in the first week. 7.5 mg. per day (30 mg.) for 4 days were given the second week. Oral ulcers developed after the second week, and attempts to increase the dose resulted in recurrent buccal ulcerations. The patient was finally stabilized on 25 mg./week (5 mg. for 5 days a week) without toxicity. Prednisone was continued at 20 mg./day.

After 1 month of therapy enzymes had fallen to SGOT 80, SGPT 34, LDH 980, CPK 1530, aldolase 16, but muscle strength had not improved. After 3 months, SGOT 27, SGPT 10, LDH 1230, CPK 500, aldolase 8.3, and muscle weakness remained unimproved. Loud crepitant rales developed in the mid to lower lung field which varied markedly from day to day, being present one day and absent the next. The patient had no pulmonary symptoms and repeated chest x-rays were negative. Pulmonary function studies demonstrated marked reduc-

tion in CO diffusing capacity with 6.11 ml./min./mm. Hg (27 per cent. predicted) as compared to 11.8 (53 per cent. of predicted) on admission. Methotrexate was discontinued for one week, and Prednisone increased to 50 mg./day, as muscle enzymes had risen sharply to SGOT 72, SGPT 27, LDH 1210, CPK 2163, aldolase 20.2. Methotrexate was re-instituted at 25 mg./week orally.

After 4 months muscle strength began to improve, although the enzymes remained elevated: SGOT 28, SGPT 21, LDH 680, CPK 350, aldolase 3.9. The pulmonary findings cleared, but the CO diffusing capacity remained low at 8.4 (37 per cent. predicted). After 5 months, the patient was able to rise from the supine position and from a chair. All enzymes became normal at 9 months, and normal muscle strength was regained at 11 months. Prednisone had been tapered to 20 mg./day. The patient continues to do well on maintenance Methotrexate 25 mg./week and prednisone 20 mg./day.

Case 5, a 69-year-old retired manual labourer, had been in excellent health except for a peptic ulcer treated medically in 1962. Approximately 1 year before admission he noted the insidious onset of weakness in the lower extremities. During the 4 months before admission, in April, 1970, a 40 lb weight loss occurred. At no time did he experience muscle pain, dysphagia, skin rash, or Raynaud's phenomenon.

Physical examination

The patient was an obese black man in no distress. There was 1+ bilateral pretibial oedema. Moderate weakness in the quadriceps and iliopsoas was noted bilaterally. Minimal weakness was present in the proximal muscles of the upper extremities and neck. No muscle tenderness was detected. The other results of the examination were within normal limits.

Laboratory investigations

Haematocrit 49 per cent.; WBC 4300/mm³ with normal differential; platelets 130,000/mm³; erythrocyte sedimentation rate 10 mm./hr. Thyroid function studies normal. Tests for rheumatoid factor and antinuclear antibodies negative. SGOT 40, SGPT 24, CPK 174, aldolase 2.9. Electromyogram showed only non-specific changes. Biopsy of the left quadriceps contained a small number of degenerating and regenerating myofibrils with interstitial chronic inflammation.

A search for malignancy was negative. Although an upper gastrointestinal series demonstrated a large gastric ulcer on the lesser curvature, brushings for cytology were negative.

The patient refused gastric surgery and after one month of an intensive medical regimen, the upper gastrointestinal series was normal.

Course

The patient was then given prednisone 60 mg./day for polymyositis, and the antacid programme was intensified. After 10 days of corticosteroid therapy, abdominal pain developed. The patient refused further corticosteroid therapy and returned home in June, 1970.

During the next 4 months muscle weakness progressed in the lower extremities and increasing weakness in the right arm developed. He was re-admitted in October, 1970,

unable to sit up or walk without assistance. There was mild weakness of the biceps and triceps muscles, but deltoid strength was normal. Muscle enzymes were elevated: SGOT 80, SGPT 76, LDH 420, CPK 131. A repeat upper gastrointestinal series was normal.

Prednisone 40 mg./day was begun and there was no recurrence of abdominal pain. After 2 weeks muscle strength began to improve, and enzymes were normal. He was discharged on 30 mg. prednisone/day. Over the next 2 months, muscle strength deteriorated, muscle enzymes became elevated, and symptoms of peptic ulcer developed.

He was re-admitted in January, 1971, with muscle weakness and the following enzymes: SGOT 39, SGPT 41, LDH 500, CPK 153. An upper gastrointestinal series demonstrated a recurrence of the ulcer crater. Prednisone was tapered to 15 mg./day and intravenous Methotrexate 50 mg. weekly was begun. After 3 weeks a gingival ulcer developed, but which resolved spontaneously. After 11 weeks, he noted pruritis without any skin eruption which continued despite reduction of Methotrexate to 25 mg. weekly. After 14 weeks of therapy with a total dose of 600 mg., Methotrexate was discontinued with neither clinical nor chemical response.

Case 6, a 59-year-old technologist, had a history of excellent past health. In April, 1971, he noted aching in the anterior thighs, difficulty in rising from the supine or sitting position, inability to climb stairs, and intermittent dysphagia. Diffuse swelling and stiffness of the hands developed. No Raynaud's phenomenon occurred.

He was admitted to another hospital in June, 1971, with documented limb girdle weakness. SGOT 360, SGPT 210, LDH 2000, CPK > 70. Muscle biopsy showed inflammatory myositis without evidence of vasculitis. No evidence of malignancy was found after intensive search.

Prednisone 40 mg./day was begun and tapered to 20 mg. after 2 months. Muscle strength did not improve, muscle enzymes remained elevated, and he was admitted to The Good Samaritan Hospital in August, 1971.

Physical examination

He was acute and chronically ill, and unable to move without assistance. There was non-pitting oedema over the dorsum of the hands and pitting brawny oedema of the lower extremities. The skin was coarse and thickened over the hands and distal forearms but was not bound down. Bilateral axillary adenopathy was present. Thoracic expansion was diminished but examination of the chest was otherwise normal. There was marked muscle weakness and wasting in the strap muscles of the neck, trapezii, deltoids, biceps, triceps, iliopsoas, and quadriceps. The biceps and triceps were tender bilaterally. He was otherwise normal.

Laboratory investigations

Haematocrit 43 per cent.; WBC 13,000/mm³ with normal differential; platelets 202,000/mm³. Erythrocyte sedimentation rate 10 mm./hr. Latex-fixation, L.E. cell, and immuno-fluorescent antinuclear antibody tests negative. Chest x-ray and electrocardiogram normal. Skin biopsy from the dorsum of one hand demonstrated only actinic keratoses. All muscle enzymes were elevated: SGOT 64, SGPT 46, LDH 1335, CPK 382, aldolase 10.6. A cine

oesophagogram demonstrated weakness of the pharyngeal musculature and delayed relaxation of the cricopharyngeus with aspiration into the trachea.

Course

Prednisone 50 mg./day was begun. After 10 days of corticosteroid therapy, there was no clinical or chemical response. In view of the patient's marked debilitation, Methotrexate therapy was initiated with a 10 mg. intravenous injection followed after 1 week with 25 mg. and thereafter 50 mg. weekly. Muscle strength began to improve, and the patient was discharged.

After 6 weeks there was still proximal weakness on testing, but he could walk with support and could rise from a low chair. Muscle enzymes were still elevated: SGOT 64, SGPT 50, LDH 890, CPK 215. Because the white blood count had fallen to 6000/mm.³, the dose of Methotrexate was lowered to 25 mg.

After a week he had returned to work for 4 hours per day. Muscle strength continued to improve. With difficulty

in maintaining the intravenous route, Methotrexate was changed to 5 mg./day orally 5 days a week.

After 10 weeks of therapy he was walking without support although the LDH and CPK remained elevated at 460 and 109, respectively. He was found to have oral ulcers on the left upper dental margin and Methotrexate was discontinued. The white blood count was 8800/mm.³. After 3 days he awoke with chills and fever of 104°F., and was re-admitted to hospital. He was alert and co-operative, with temperature 105°F, pulse rate 122, respiration 26, and blood pressure 155/90. Multiple gingival and buccal ulcers were present. There were diffuse, dry, crepitant, end-inspiratory rales in both lung fields, without evidence of consolidation or effusion. There was no cyanosis. Except for diminished muscle strength proximally, the remainder of the examination was normal.

Laboratory tests included haematocrit 48 per cent., WBC 8,700/mm.³ with 9 per cent. bands, 74 per cent. segmented neutrophils, 10 per cent. lymphocytes, 6 per cent. monocytes, and 1 per cent. eosinophils. Platelets

FIG. 1(a) *Chest x ray of Case 6 at presentation with probable Methotrexate pneumonitis. Bilateral interstitial pneumonitis is present.*

FIG. 1(b) *Same patient 48 hrs after admission. Super infection with Gram-negative organisms has occurred, and the pneumonitic process had spread to multiple lobes.*

159,000/mm³. Chest x-ray revealed bilateral interstitial pulmonary infiltrates (Figs 1a and b). A transtracheal aspirate was devoid of white blood cells and no bacteria, mycobacteria, or fungi were seen. Blood and aspirate cultures were negative.

For the first 24 hours his temperature was controlled with a hypothermia blanket. Corticosteroids were continued at 50 mg./day, and he remained stable. On the

second day in hospital, he experienced a shaking chill. His temperature rose to 104° F, and tachypnea developed. Arterial blood gases revealed PO₂ 41, PCO₂ 32, pH 7.44, and bicarbonate 19.7. Blood cultures at this time and subsequently grew *E. coli* and *Pseudomonas aeruginosa*. A left percutaneous lung biopsy revealed an intense acute inflammatory process involving the interstitium (Figs 2a and b).

FIG. 2 (a) Percutaneous lung biopsy of same patient with presumed Methotrexate pneumonitis. There is an intense interstitial and alveolar inflammatory response. Haematoxylin and eosin. $\times 150$

FIG. 2 (b) Higher magnification of same lung biopsy, showing the inflammatory response to be both polymorphonuclear and mononuclear with many plasma cells. Haematoxylin and eosin. $\times 500$

Stains for bacteria, fungi, and *Pneumocystis* were negative.

He was intensively treated with positive pressure oxygenation and antibiotics. The pulmonary infiltrates became more diffuse and sputa grew *Pseudomonas*. Despite intensive care over the next 6 weeks, the infection could not be eradicated, and oxygenation could not be maintained.

Termination

The patient expired on December 22, 1971. Permission for post mortem examination was not obtained.

Analysis of clinical data

When these five Methotrexate-treated patients (Cases 3–7) are compared to those requiring steroids alone, several striking clinical and laboratory features become apparent (Table I).

First, clinically, these patients had lost more muscle strength and mass, and their disease was more rapidly progressive than in the other eleven patients. Furthermore, if calculable, an average maintenance dose of Prednisone would have exceeded 40 mg./day as compared to an average maintenance dose of 20 mg./day in those controlled by steroids alone.

Four of the five had polymyositis alone, representing 66 per cent. of Group I. The fifth patient was one of six patients with systemic sclerosis, the remainder of Group II (except for Case 13) responding to corticoids alone. The myopathy in two patients (Group III) with tumour syndromes improved promptly on corticosteroids, including Case 16 whose enzymes had returned to normal before neoplasm resection.

Age, sex, race, and duration of symptoms did not correlate with steroid resistance.

On chemical grounds, the Methotrexate-treated patients had more severe disease. The serum level of each of the muscle enzymes were higher in these five patients (Table II); furthermore, more uniform elevation of enzymes was found in them than in those with milder disease and varying enzyme patterns (Table III). As evident in the steroid-treated patients, the SGOT and CPK were most sensitive, each being elevated in 81 per cent. of those tested. Less sensitive were the SGPT (36 per cent.), the LDH (55 per cent.), and the aldolase (50 per cent.). Of interest, but unexplained, was a transient initial rise in aldolase in three of six patients.

Of these patients with more severe and progressive

Table I *Particulars of sixteen patients*

Group no.	Patient no.	Age	Race	Sex	Duration before corticosteroid therapy (mths)	Prednisone therapy (mg/day)		Duration of corticosteroid therapy (mths)
						Maximal	Maintenance	
I	1	72	B	F	0.5	60	10	8
	2	51	B	M	16.0	40	20	31
	3*	69	W	M	4.0	100	>60	7
	4*	47	B	F	2.0	80	>30	17
	5*	69	B	M	18.0	40	>40	4
	6*	59	W	M	3.0	50	>50	3
II	7*	19	B	F	6.0	80	>20	18
	8	60	B	M	3.0	30	15	20
	9	53	B	M	2.0	40	25	15
	10	25	B	F	5.0	40	15	3
	11	43	B	F	4.0	30	30	11
	12	30	B	F	6.0	40	15	24
	13	54	B	M	108.0	> 60	0	8
	14	47	W	F	9.0	60	15	20
III	15	73	B	M	11.0	30	20	4
	16	48	W	F	10.0	40	25	4

* Methotrexate-treated patients.

disease, one (3) was steroid-refractory, and three (4, 7, 5) required higher dosage levels of prednisone than could be tolerated. The final patient (6) had fulminant disease which did not permit any therapeutic trial on steroids alone.

The response to therapy was determined by two criteria, namely, improvement in muscle strength and return to normal of elevated muscle enzymes (Table IV). Of the five patients, three improved and one showed no response. The remaining patient was treated concomitantly with high-dose steroids and Methotrexate, and his improvement could be attributed to either or both drugs, since he had previously received steroids only in low dosage with little benefit. Two patients regained normal muscle strength, and significant improvement oc-

curred in two. The muscle enzymes reverted to normal in three patients and were progressively declining in the patient (6) who died. Only one patient (5) demonstrated no significant change, clinically or chemically.

Maximal muscle strength had returned at 5 weeks (after a dosage of 125 mg.) in one, 14 weeks (575 mg.) in another, and 44 weeks (1,060 mg.) in the one patient treated exclusively by the oral route.

Normal enzymes levels occurred as early as 10 weeks and, in the patient on oral therapy as late as 36 weeks. In two patients (3, 7) the chemical response antedated the time of maximal muscle strength; and in the third (4), the reverse was true.

It was necessary to discontinue Methotrexate in three patients because of complications. One patient

Table II Muscle enzymes levels

Therapy	No. of cases		SGOT	SGPT	LDH	CPK	Aldolase
Steroids and Methotrexate	5	Mean Range	243 40-575	90 24-210	1162 500-2000	1752 174-4471	16.4 2.9-30.7
Steroids alone	11	Mean Range	87 14-320	41 2-110	390 95-930	381 30-1170	11.8 1.7-31

Table III Muscle enzymes elevated

Therapy	Proportion of patients with enzyme elevation				
	SGOT	SGPT	LDH	CPK	Aldolase
Steroids and Methotrexate	5/5	4/4	3/3	5/5	3/4
Steroids alone	9/11	4/11	5/9	9/11	3/6

Table IV Methotrexate therapy

Case no.	Response (a, b)*	Total dosage (mg.)	Duration (wks)	Maintenance prednisone achieved	Complications
3	a—Improved b—Normal	575 i.v. 375 i.v.	14 10	15	Stomatitis Hepatotoxicity
4	a—Normal b—Normal	125 i.v. 275 i.v.	5 11	25	None
7	a—Normal b—Normal	1060 oral 790 oral	44 36	20	Stomatitis (?) Methotrexate lung
5	a—No change b—No change	600 i.v. when drug disc. at 14 wks		15	Stomatitis Pruritis
6	a—Improved b—Improved	360 i.v. and oral when drug disc. at 10 wks		50	Stomatitis Methotrexate lung Died

a—Muscle strength.
b—Serum enzymes.
i.v. = intravenous.

(3) had achieved maximal benefit and was on maintenance drug when it was stopped at 32 weeks because of hepatotoxicity. Another (5) developed pruritis and refused further therapy after 14 weeks (600 mg.), no benefit having been achieved. In a third patient (6), Methotrexate was discontinued at 10 weeks (360 mg.) in view of probable Methotrexate pneumonitis, although his muscle strength and enzymes had shown marked improvement.

Discussion

Although the aetiology and pathogenesis of polymyositis are still ill-defined, evidence is mounting in support of immunologically-mediated tissue injury. Several investigators have reported observations of altered cell-mediated immunity (Currie, Saunders, Knowles, and Brown, 1971; Saunders, Knowles, and Currie, 1969; Currie, 1970). More recently, Whitaker and Engel (1972) have emphasized the role of immune-complex deposition by virtue of their demonstration in the vessel walls of skeletal muscle of granular deposits containing immunoglobulins (IgG and IgM) and complement. Clinically, polymyositis is not associated with autoantibodies to nuclear antigens and altered gamma globulin but may also be the dominant manifestation of such immune disorders as systemic lupus erythematosus and Sjögren's syndrome.

Thus, there is a reasonable basis for the use of Methotrexate in the significant number of patients (31 per cent our series) who resist adequate control by corticosteroids alone, as it is one of the agents with established immunosuppressive properties (Berlin, Rall, Mead, Freireich, Van Scott, Hertz, and Lipsett, 1963; Rivarola, Friedman and Lawrence, 1967) as well as an anti-inflammatory action (Hersh, Wong, and Freireich, 1966).

Malaviya and others (1968) first reported the successful treatment of dermatomyositis with Methotrexate alone (one patient) or in combination with corticosteroids (three patients). Dramatic response was noted in each of the four patients within 1 month; and, with continued weekly intravenous therapy, complete remission was achieved in three. Similarly, Sokoloff and others (1971) reported improvement (marked in one, moderate in four) in five of seven patients. Maximal response was observed between 9 and 19 weeks, after a total dosage of 460 to 825 mg. had been administered intravenously at the rate of 0.8 mg./kg./body weight/week.

As in these previous reports, Methotrexate was found to be therapeutically effective in four of our five patients. The single patient (5) who failed to improve clinically or chemically was otherwise separable from the Methotrexate-responsive group with respect to the prolonged interval (19 months) of

active disease before the institution of corticosteroid therapy, as compared to periods of 2 weeks to 6 months in the others.

The time and total dosage required to effect optimal improvement in our patients receiving intravenous therapy was entirely comparable to the course observed by earlier investigators (Malaviya and others, 1968; Sokoloff and others, 1971). The marked increase in lag time before therapeutic response in the patient (7) necessarily receiving oral Methotrexate (5 mg./day, 5 days/week) is difficult to understand, for patient 4, receiving the same weekly dose of 25 mg. (but intravenously) had achieved normal strength in five weeks and normal enzymes levels in eleven. There does not appear to be a well-defined maximal or minimal dose at which improvement occurs; similarly, toxic manifestations are not dose-related. In contrast to the earlier reports, toxicity was of major concern in our patients. The most frequent was stomatitis, observed in four and most marked and dose-limiting in the two who received oral drug. Chemical hepatitis and pruritis were each observed in one instance. In none was marrow suppression observed. Most serious and also seemingly related to oral administration was probable Methotrexate pneumonitis in two patients, contributing to death in one. There is evidence that oral Methotrexate, administered daily, has greater toxicity than weekly intravenous therapy, probably because of the higher sustained blood levels and less rapid excretion (Mitchell, Wade, DeConti, Bertino, and Calabresi, 1969; Zurek, Ojima, Anderson, Collins, Oberfield, and Sullivan, 1968).

To date, there are 54 reported cases of Methotrexate lung disease (*J. Amer. med. Ass.*, 1969; Clarysse, Cathey, Cartwright, and Wintrobe, 1969; Schwartz and Kajani, 1969; Pasquinucci, Ferrara, and Castellari, 1971; Robertson, 1970; Filip, Logue, Harle, and Farrar, 1971; Goldman and Moschella, 1971), all in patients receiving oral or intramuscular therapy; 51 of them had acute lymphocytic leukaemia, in each instance in remission on Methotrexate when the pneumonitic process emerged. The remaining three patients were being treated for dermatological disorders (Filip and others, 1971; Goldman and Moschella, 1971). Although the Methotrexate lung syndrome was characterized by severe and acute illness with high fever, cough, dyspnoea, hypoxaemia, and pneumonitis, only three (6 per cent) deaths were reported. Response was usually prompt to withdrawal of the drug and, in severe cases, to the institution of corticosteroid therapy as well. In those cases reported earlier, there was no apparent critical dosage level or duration of therapy related to development of this complication. The radiological picture has been that of a diffuse, bilateral interstitial pneumonitis, more impressive than clinical signs would predict. Three lung biopsies have been re-

corded and have demonstrated diffuse lymphocytic infiltration, interstitial and alveolar, with giant cells and non-caseating granulomata.

One, and possibly two, of our patients seemed to show pulmonary toxicity from Methotrexate. In the patient (7) with less certain findings, we were puzzled at the time by the appearance of end-inspiratory crepitant rales bilaterally which would come and go from one day to the next. Although asymptomatic and without associated radiological change, pulmonary function tests did show deterioration with respect to diffusion capacity. Not suspecting Methotrexate toxicity, the drug was continued, and the auscultatory findings disappeared, and pulmonary function improved after corticosteroids were increased. The variability of chest findings initially plus the response to corticosteroids support an inflammatory process as opposed to progression of systemic sclerosis, and a *forme fruste* of Methotrexate pneumonitis remains highly suspect.

The second patient (6) was in his third week of oral Methotrexate therapy (10th week on the drug) when, first buccal ulceration and then hyperpyrexia and rapidly progressive diffuse pneumonitis appeared. Chest X rays (Figs 1a and b) and lung biopsy (Figs 2a and b) were compatible with Methotrexate pneumonitis, although histologically no giant cells or granulomata were found. All bacteriological cultures, including the lung on biopsy, were initially sterile, although virus studies could not be made. Subsequent superinfection and death followed in several weeks despite withdrawal of Methotrexate, massive

antibiosis, augmented steroids, and ventilatory assistance.

While the number of patients is small, our experience supports previous reports that Methotrexate may prove efficacious in some patients with polymyositis who cannot be controlled with tolerable levels of steroids alone. However, in contrast to previous authors who consider Methotrexate a relatively safe drug, we find that the toxicity is appreciable and may be severe in those patients who are given the drug by mouth. Certainly, Methotrexate should be reserved for only those individuals with steroid-refractory disease who can be placed on a weekly intravenous regimen under close observation, especially with respect to the pulmonary status.

Summary

Five of sixteen patients with polymyositis, whose disease could not be controlled with corticosteroids alone, received Methotrexate therapy. Four had pure polymyositis while one had myositis associated with systemic sclerosis. As a group, they demonstrated, clinically and chemically, more severe muscle disease than those requiring steroids alone. Three patients clearly responded to the drug, but toxicity was a significant limiting factor. The most serious complication, namely Methotrexate pneumonitis, observed in two patients receiving oral dosage, contributed to death in one. Methotrexate therapy, while a useful adjunct in the steroid-refractory patient, is highly toxic, especially when given orally, and must be used with caution.

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